

Claims

1. A modified glucocorticoid receptor protein capable of binding a non-natural ligand, comprising a fusion protein, wherein said fusion protein comprises: a 5 glucocorticoid receptor region, wherein said region comprises a DNA binding domain and one or more transregulatory domains, wherein each said transregulatory domain is capable of transactivating or transrepressing gene expression; and a mutated progesterone receptor 10 ligand binding region, wherein said mutated progesterone receptor ligand binding region is capable of binding a non-natural ligand.

2. The modified glucocorticoid receptor of claim 1, wherein said mutated progesterone receptor ligand binding 15 region is mutated by deletion of about 16 to 42 carboxyl terminal amino acids of a progesterone receptor ligand binding domain.

3. The modified glucocorticoid receptor protein of claim 1, wherein said mutated progesterone receptor ligand 20 binding region consists essentially of amino acids 640 through 891 of a progesterone receptor ligand binding domain.

4. The modified glucocorticoid receptor protein of claim 1, wherein said mutated progesterone receptor ligand 25 binding region consists essentially of amino acids 640

through 917 of a progesterone receptor ligand binding domain.

5. The modified glucocorticoid receptor protein of claim 1, wherein said mutated progesterone receptor ligand 5 binding region consists essentially of amino acids 640 through 920 of a progesterone receptor ligand binding domain.

6. A modified glucocorticoid receptor protein comprising a ligand binding domain without ligand binding 10 activity, a DNA binding domain and transregulatory domains, wherein said transregulatory domains are capable of constitutively transactivating or transrepressing gene expression without said ligand binding activity.

7. A modified glucocorticoid receptor protein 15 capable of binding a non-natural ligand, comprising: a glucocorticoid receptor region, wherein said region comprises a DNA binding domain and a mutated transregulatory domain, wherein said transregulatory domain is capable of transactivating but not 20 transrepressing gene expression; and a mutated ligand binding domain.

8. A modified glucocorticoid receptor protein capable of binding a non-natural ligand, comprising: a glucocorticoid receptor region, wherein said region 25 comprises a mutated DNA binding domain and transregulatory

domains, wherein said transregulatory domains are capable of transrepressing but not transactivating gene expression; and a mutated ligand binding domain.

9. A modified glucocorticoid receptor protein  
5 capable of binding a non-natural ligand, wherein said protein comprises a DNA binding domain, transregulatory domains and a mutated ligand binding domain, wherein said mutated ligand binding domain is mutated by deletion of about 2-5 carboxyl terminal amino acids from the ligand  
10 binding domain and capable of binding a non-natural ligand.

10. The modified glucocorticoid receptor protein of claim 9, wherein said protein is mutated by deleting amino acids 762 and 763 of the ligand binding domain and  
15 changing amino acid at position 752 to alanine and amino acid at position 753 to alanine.

11. A nucleic acid sequence encoding a modified glucocorticoid receptor protein of 1, 6, 7, 8 or 9.

12. A vector containing a nucleic acid sequence  
20 encoding for a modified glucocorticoid receptor protein of 1, 6, 7, 8 or 9, wherein said vector is capable of expressing said modified glucocorticoid receptor protein.

13. A cell transfected with a vector of claim 12.

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C1  
C1*

14. A cell transformed with a vector of claim 12.

15. A method of using a modified glucocorticoid receptor protein comprising the steps of transforming a cell with a vector of claim 12, wherein said transformed cells express said modified glucocorticoid receptor protein and said modified glucocorticoid receptor protein is capable of regulating the expression of glucocorticoid responsive genes by a non-natural ligand.

16. The method of claim 15, wherein said non-natural ligand is RU486.

17. The method of claim 15, wherein said regulation is transactivation of glucocorticoid responsive genes.

18. The method of claim 15, wherein said regulation is transrepression of NF<sub>K</sub>-B and AP-1 regulated genes.

19. The method of claim 15, wherein said transformed cell is selected from the group consisting of a muscle cell, lung cell or a synovial cell.

20. A method of treating arthritis comprising the steps of transforming cells associated with the joints in situ with a vector of claim 12 encoding a mutated glucocorticoid receptor protein, wherein said transformed cells express said mutated glucocorticoid receptor protein and said mutated glucocorticoid receptor protein is

capable of regulating the expression of glucocorticoid responsive genes by a non-natural ligand.

21. The method of claim 20, wherein said non-natural ligand is RU486.

5 22. The method of claim 20, wherein said regulation is transactivation of glucocorticoid responsive genes.

23. The method of claim 20, wherein said regulation is transrepression of NF<sub>K</sub>-B and AP-1 regulated genes.

24. A method of treating asthma comprising the steps  
10 of transforming lung cells *in situ* with a vector of claim  
12 encoding a modified glucocorticoid receptor protein,  
wherein said modified glucocorticoid receptor protein  
expressed in said transformed cell is capable of  
regulating expression of glucocorticoid responsive genes  
15 by a non-natural ligand.

25. The method of claim 24, wherein said non-natural ligand is RU486.

26. The method of claim 24, wherein said regulation is transactivation of glucocorticoid responsive genes.

20 27. The method of claim 24, wherein said regulation is transrepression of NF<sub>K</sub>-B and AP-1 regulated genes.

28. A method of making a transformed cell *in situ* comprising the step of contacting said cell with a vector of claim 12 for sufficient time to transform said cell, wherein said transformed cell expresses a modified glucocorticoid receptor protein encoded by said vector.

29. A transgenic animal whose cells contain a vector of claim 12.

30. A plasmid designated as pGR0403R.

*Subj2* 31. A cell transformed with a plasmid of claim 30.

10 32. The modified glucocorticoid receptor protein of claim 1, wherein said mutated progesterone ligand binding region consists essentially of amino acids 640 through 914 of a progesterone receptor ligand binding domain.

15 33. The modified glucocorticoid receptor protein of claim 1, wherein said transregulatory domain is located in the N-terminal region of said mutated progesterone ligand binding domain.

20 34. The modified glucocorticoid receptor protein of claim 1, wherein said transregulatory domain is located in the C-terminal region of said mutated progesterone ligand binding domain.

35. The modified glucocorticoid receptor protein of claim 7, wherein said modified glucocorticoid receptor protein activates target gene expression.

36. The modified glucocorticoid receptor protein of 5 claim 1, wherein said DNA binding domain is a GAL4 DNA binding domain.

37. The modified glucocorticoid receptor protein of claim 35, wherein said target gene encodes nerve growth factor.

10 38. The modified glucocorticoid receptor protein of claim 1, wherein said transregulatory domain comprises a Krüppel-associated box-A (KRAB) transrepressing domain.

39. The modified glucocorticoid receptor protein of claim 1, wherein said mutated progesterone receptor ligand 15 binding region is capable of responding to RU486 at a concentration as low as 0.01 nM.

40. A modified steroid hormone receptor protein, wherein said receptor responds to a conventional antagonist of the wild-type steroid hormone receptor 20 protein counterpart with an agonistic response.

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